Early onset depression: characterising developmental trajectories and the role of neuropsychiatric genetic risk variants

Rice, F., Riglin, L., Thapar, A.K., Heron, J., Anney, R., O'Donovan, M.C., Thapar, A.

Key points

Question: Do neuropsychiatric disorder genetic risk variants influence developmental trajectories of depression in youth?

Findings: Distinct depression trajectory classes were identified. A late-adolescent-onset class (17.3% of the sample) showed a typical depression trajectory and was associated with major depressive disorder risk alleles. An early-adolescent-onset class (9.0%) showed clinically significant symptomatology at age 12 and was associated with neurodevelopmental, schizophrenia and ADHD, risk alleles and childhood neurodevelopmental traits.

Meaning: Depression in youth is highly heterogeneous. Findings are consistent with emerging evidence for a neurodevelopmental component to some cases of depression and that this is more likely when onset is very early.

Abstract

Importance

Depression often first manifests in adolescence. Thereafter individual trajectories vary substantially but it is not known what shapes depression trajectories in youth. Adult studies suggest that genetic risk for schizophrenia, a psychiatric disorder with a neurodevelopmental component, may contribute to earlier onset depression.

Objective

To test the hypothesis that there are distinct trajectories of depressive symptoms and that genetic liability for neurodevelopmental psychiatric disorders (schizophrenia, ADHD), as well as for Major Depressive Disorder (MDD), contribute to early-onset depression.

Design, setting and participants

The ALSPAC (Avon Longitudinal Study of Parents and Children) study is an ongoing prospective longitudinal population-based cohort that has been collecting data since September 1990 including 7543 adolescents with data on depressive symptoms at multiple time points.

Main outcome measures

Trajectories based on self-reported depressive symptoms dichotomised by the clinical cut-point. MDD, schizophrenia and Attention Deficit Hyperactivity Disorder (ADHD) polygenic risk score (PRS) were predictors.

Results

In 7543 adolescents with depression data on more than one assessment point between age 10.5 years (mean age 10.64, SD=.25) and 18.5 years (3568 male; 3975 female), three trajectory classes were identified: persistently low (73.7%), late-adolescent-onset (17.3%), and early-adolescent-onset (9.0%). The late-adolescent-onset class was associated with MDD genetic risk only (OR $_{\text{MDD PRS}}$=1.27, 95% CI, 1.09-1.48, p=.003). The early-adolescent onset class was also associated with MDD genetic risk (OR $_{\text{MDD PRS}}$=1.24, 95% CI, 1.06-1.46, p=.007) but additionally with genetic risk for neurodevelopmental disorders (OR $_{\text{schizophrenia PRS}}$

= 1.22, 95% CI, 1.04-1.43, p=.013; $OR_{ADHD\ PRS}$ =1.32, 95% CI, 1.13-1.54, p<.001) and childhood ADHD and neurodevelopmental traits.

Conclusions and relevance

We found evidence of distinct depressive trajectories, primarily distinguished by age-at-onset. The more typical depression trajectory with onset of clinically significant symptomatology at age 16 was associated with MDD genetic risk. The less common depression trajectory, with a very early onset, was particularly associated with ADHD and schizophrenia genetic risk and, phenotypically, with childhood ADHD and neurodevelopmental traits. Findings are consistent with emerging evidence for a neurodevelopmental component to some cases of depression and suggest this is more likely when onset is very early.

Keywords: neurodevelopmental, ADHD, depression, schizophrenia, longitudinal, trajectory, ALSPAC, genetic, polygenic

Introduction

Major depressive disorder (MDD) is the most common mental disorder and a leading cause of disability[1], even subthreshold depressive symptoms are associated with functional impairment and future mental health problems[2,3]. Depression often first manifests in adolescence[4-6] and thereafter, individual trajectories of depressive symptomatology vary substantially[7]. A family history of depression and an early age-of-onset are each associated with a more chronic symptom course in adults with MDD[8-10] but it is not known what shapes early depression trajectories in youth.

Depression has a complex multifactorial etiology including a moderate heritable component[4,11,12]. Longitudinal and family studies show strong continuity between both adolescent-onset depressive disorder and symptoms with depression in adult life, but there are also developmental differences between depression in children, adolescents and adults[4]. For instance, clinical follow-up studies of very early-onset depression (average age-of-onset=10.7 years) report high rates of heterotypic continuity, where, depression is often followed by a different type of clinical disorder[13-15]. Twin studies also show differences in the genetic etiology of very early-onset depressive symptoms compared to those arising in mid to late adolescence[16-18]. At the molecular level, a recent genome-wide association study (GWAS) of adults with MDD found evidence of differences in the genetic architecture of depression where a *relatively* early age-of-onset (before the median age-of-onset of 27 years) was associated with genetic liability to schizophrenia, an association not seen for later-onset depression which was instead associated with MDD risk alleles[19]. Similar findings have been reported for emotional problems (symptoms of depression and anxiety) in that emotional problems in childhood were associated with schizophrenia risk alleles but in adult life they were additionally associated with MDD genetic risk[20]. The association of schizophrenia risk alleles with childhood emotional problems was particularly pronounced in those with emotional problems in both childhood and adulthood suggesting that persistent emotional symptoms beginning early may drive the association with schizophrenia risk

alleles. As schizophrenia genetic risk is thought to involve an early neurodevelopmental component[21,22], the role of genetic risk for other neurodevelopmental disorders in early-onset depression may be important to consider. In particular, genetic risk for ADHD, a common childhood-onset neurodevelopmental disorder, may be important in early-onset depression because cross-sectional and longitudinal cohort studies show heighted rates of depression in children with ADHD[23-25] which may be partly due to the strong genetic correlation between ADHD and depression (r_g= .424)[26,27].

Here we test the contribution of neuropsychiatric disorder genetic risk variants, specifically genetic liability to MDD, schizophrenia and ADHD, to early depression trajectories. Schizophrenia and ADHD were selected in addition to MDD as they show moderate to high genetic correlations with major depression[27], there is evidence linking schizophrenia PRS to early-onset depression[19,20] and epidemiological and clinical evidence[15,23-25] that ADHD may be an important antecedent of depression. Estimates of genetic liability to the disorders in the form of polygenic risk scores were derived from risk alleles defined in the largest available GWAS of those disorders. We did not have a specific hypothesis for bipolar disorder genetic risk because existing studies reporting conflicting results about the phenotypic relationship between early-onset depression and bipolar disorder[13,15,28] with little evidence that this is stronger for early-onset depression. Bipolar disorder also differs from ADHD and schizophrenia in that evidence suggests it is less neurodevelopmental in origin[21,22]. However, for completeness we included bipolar polygenic risk scores in our analyses (eTable2a). We hypothesised that ADHD and schizophrenia genetic risk would show association with early-onset depression. We hypothesised that depression genetic risk would be associated with depression with an onset later in adolescence.

Methods

The Avon Longitudinal Study of Parents and Children (ALSPAC) is an ongoing population-based prospective longitudinal UK birth cohort[29,30]. Data collection began in September 6th,

1990. The enrolled core sample consisted of 14,541 pregnant women living in Avon, England, with expected delivery dates between April 1, 1991, and December 31, 1992. Of these, 13,988 children were alive at 1 year. An additional 713 children who would have been eligible but whose mothers did not enrol during pregnancy were enrolled after age 7 years giving a total sample of 14,701 alive at 1 year. Ethical approval for the study was obtained from the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees. All participants provided written informed consent. The study website contains details of all the data that is available through a fully searchable data dictionary (http://www.bristol.ac.uk/alspac/researchers/access/). For families with multiple births, we included the oldest sibling. Individuals were included in analyses when data on the primary outcome of depressive symptoms were available for at least two time points (N=7543). Numbers of individuals with data available at different time points are in Figure 1 (Supplement).

Depressive symptoms were reported by the young person at six time points (ages 10.5, 12.5, 13.5, 16.5, 17.5 and 18.5 years) on the short Mood and Feelings Questionnaire (sMFQ). This is a well-validated symptom checklist[31-33] which includes 13 items about mood symptoms during the past 2-weeks (rated 0 (not true), 1 (sometimes true) or 2 (true); score range 0-26). Scores above 11 represent clinically significant symptoms[31,33] and we analysed individuals scoring above and below this to examine trajectories of clinically significant symptomatology.

Polygenic risk scores (PRS) for MDD, schizophrenia, and, ADHD were generated in study individuals as the standardized mean number of disorder risk alleles in approximate linkage equilibrium ($R2<0.20$), weighted by genome-wide association study allele effect size, derived from data of imputed autosomal single-nucleotide polymorphisms. All packages used in this analysis used Stata 13.0 to implement the PLINK toolset (http://zzz.bwh.harvard.edu/plink/). Code is available at https://github.com/ricanney/stata. In brief, best guess genotype

underwent additional marker and individual quality control. Individuals were excluded on the basis of excessive heterozygosity (> 4 standard deviations (SD) from sample mean), relatedness (> 3 SD from sample mean) and genotype missingness (>2%). Markers were excluded if they were rare, (minor allele count less than 5), had high levels of missingness (>2%) or deviated from Hardy-Weinberg equilibrium ($p \leq 10^{-10}$) or from reference MAF (>10%) (Supplement).

Scores were derived from MDD, ADHD and schizophrenia weights for 152,536, 103,041 and 27,336 SNPs respectively. Risk alleles were defined as those associated with case status in the most recent Psychiatric Genomics Consortium analyses of MDD, ADHD and schizophrenia at a threshold of $P < .50$ for depression and ADHD and $P < .05$ for schizophrenia as these thresholds maximally capture phenotypic variance[26,27,34-36]. Genome-wide association study discovery sample sizes were: 130,664 cases and 330,470 controls for MDD, 20,183 cases and 35,191 controls for ADHD, and 35,476 cases and 46,839 controls for schizophrenia. All PRS were standardized prior to analysis so odds ratios represent one standard deviation change. (eTable 2a for bipolar PRS).

Phenotypic measures of neurodevelopmental problems (DSM-IV[37] diagnoses of childhood ADHD, social communication problems and pragmatic language difficulties at age 7), psychotic experiences (ages 12 and 17) family history of severe depression and schizophrenia and maternal education were used (eAppendix).

Analysis

We characterised depression trajectories of symptoms dichotomised by clinical cut-point (N=7543) using latent class growth analysis (LCGA) in Mplus version 8[38]. This is a probability-based technique used to identify an optimum number of distinct patterns (classes) of growth (change) in the longitudinal depression scores of individuals[39] . Models were run with increasing numbers of classes starting with a one-class solution specifying

both linear and quadratic change with 500 random starting values and 50 optimisations. Residual variances were allowed to vary across measurement points. A maximum likelihood parameter estimator for which standard errors are robust to non-normality (MLR) was used. To examine associations with categorical variables e.g. gender, the DCAT auxillary option in MPlus was used. A bias-free three step approach in MPlus (R3STEP) estimated the associations between continuous hypothesised predictor variables (PRS) and trajectory class[40,41,42]. Model selection was informed by model fit indices and interpretability as recommended[43]. Full Information Maximum Likelihood (FIML) estimation was used in MPlus and included all individuals with more than one depression assessment in analyses (eTable 1). For tests of PRS association with trajectory class, we re-ran analyses using inverse probability weighting (IPW)[44] to address any potential bias caused by participant dropout. The pattern of results was similar (eTable 4).

Results

Depression symptom trajectories

A three class trajectory model provided the best fit to the data and provided results that were most readily interpretable (eTable 1). Figure 1 shows the three distinct trajectory classes – a persistently low class (73.7%), a late-adolescent-onset class (17.3%), and an early-adolescent-onset class (9.0%). In the early-adolescent-onset class, the probability of clinically significant depression was first elevated (as indicated by a probability of clinically significant depression symptoms of .44) at age 12.5 years which rose to .52 at 13.5 years. In the late-adolescent-onset class, the probability of clinically significant depression (probability =.47) was first elevated at age 16.5 years and rose at 17.5 years (.57). Both elevated trajectories were associated with a diagnosis of MDD (assessed by the CIS-R[45] at age 17.5) providing 'validation' of the trajectory classes (late-adolescent-onset 34.4%; early-adolescent onset 22.8%, low 1.5%, overall difference $\chi^2_{(2)}$=193.70, p=.001). The estimated proportion of females was 45.8% in the low class and was higher but did not differ between the early-adolescent (74.3%) and late-adolescent-onset classes (73.2%) (Table 2).

Neuropsychiatric PRS and trajectory class

As shown in Table 1, the late-adolescent-onset class was associated with higher MDD PRS only (OR=1.27, 95% CI=1.09, 1.48, p=.003). The early-adolescent-onset class was associated with higher ADHD, schizophrenia and MDD PRS (OR ADHD PRS =1.32, 95% CI=1.13, 1.54, p<.001; OR schizophrenia PRS =1.22, 95% CI=1.04, 1.43, p=.013; OR MDD PRS = 1.24, 95% CI=1.06, 1.46, p=.007). Post-hoc, we examined the association with all three psychiatric PRS and trajectory class to examine which PRS contributed most strongly (Table 1). As expected the PRS were correlated (eTable 2b). Multivariate analysis showed that the strongest association with the early-adolescent-onset class was observed for ADHD PRS, that the association with schizophrenia PRS was retained, and that the association with MDD PRS became non-significant (Table 1). Results for the late-adolescent-onset class remained the same. Bipolar PRS was not associated with trajectory classes (eTable 2a). Including ancestry derived principal components did not alter results (eTable 3).

We tested whether the trajectory classes differed phenotypically on traits conceptually related to ADHD PRS (childhood ADHD and neurodevelopmental traits) and schizophrenia PRS (psychotic experiences). For childhood neurodevelopmental traits, there is clear evidence that this is associated with both ADHD and ADHD PRS[46,47], for psychotic experiences, there is inconsistent evidence that this is linked with psychosis and schizophrenia PRS[48,49]. (Table 2). Individuals in the early-adolescent onset class had higher rates of childhood ADHD (6.3%) than the late-adolescent onset (0.9%) and the low classes (1.7%) and more social communication and pragmatic language problems (Table 2). Proportions scoring above the standard cut points were: 20.7% early-onset, 4.2% later-onset, 5.8% low, for social communication and 13.3% early-onset, 2.1% later-onset, 1.4% low, for pragmatic language. These differences distinguished the early-adolescent and late-adolescent onset classes (Table 2). For psychotic experiences, these distinguished the early-adolescent and late-adolescent onset classes only at age 12.

Discussion

This study identified substantial variation in the developmental trajectories of depression from childhood to early adult life, and moreover, that this is partly attributable to MDD, schizophrenia and ADHD risk alleles. We found evidence of distinct depressive trajectories, primarily distinguished by age-at-onset. We found that the more common, 'typical', developmental trajectory, with onset after puberty and persistence into early-adulthood[6,50] was associated with elevated genetic risk for depression, indexed by MDD PRS. In contrast, we found that depressive symptoms defined by a very early-onset (by age 12) were associated with all neuropsychiatric genetic risk scores assessed, with the multivariate analysis showing that the association was strongest for ADHD PRS. Phenotypically, childhood neurodevelopmental difficulties (ADHD, pragmatic language and social communication difficulties) differentiated the depression trajectories which were elevated only in the early-adolescent onset group with rates increased by 5 to 7-fold in the early-adolescent onset group. Psychotic experiences differentiated the groups at age 12 only. This may be driven by depressive symptom differences between the groups at age 12 (Figure 1) given the reported association between psychotic experiences and depression and an inconsistent association with psychotic experiences and schizophrenia PRS[48,49]. The findings are consistent with a growing body of literature showing that depression has a heterogeneous etiology partly indexed by age of onset. In particular, studies of adult MDD and of symptoms measured continuously in population-based samples illustrate that a relatively earlier onset is more strongly associated with schizophrenia polygenic risk[19,20,51]. We find an additional contribution from ADHD polygenic risk scores. The implication of those results is that early and later adolescent onset depression differ to some extent with respect to the risk factors involved and that the earlier onset disorder is more strongly influenced by neurodevelopmental factors than depression with a more typical onset in later adolescence or early adulthood. This is consistent with a number of observations from epidemiological, family and clinical studies. First, several family and clinical follow-up studies suggest that

childhood-onset depression might differ etiologically from adolescent-onset depression[52-55]. Second, the epidemiology of very early-onset depression differs from that of depression with onset in mid-to-late adolescence in the gender ratio of affected individuals and long-term psychiatric outcomes[13,56]. Third, neurodevelopmental difficulties including speech abnormalities and poor motor skills are particularly associated with early-onset rather than adolescent- or adult-onset depression[15,57,58]. Fourth, substantial clinical evidence shows that children with ADHD, a common neurodevelopmental disorder, are at elevated risk of subsequent depressive symptoms, suicide attempt and emotional problems when they grow up[25,59-62]. Indeed, theory suggests neurodevelopmental difficulties as one route to emotional disturbance through the repeated experience of academic failure and peer rejection[63] although ADHD and depression may also be associated due to common risk factors[64]. A clinical issue is that the response to antidepressant medication [65-68] in youth is not as good as it is in adults and evidence suggests the response to tricylics may differ in pre-pubertal versus post-pubertal depression. One possibility is that more 'neurodevelopmental' depression shows a different type of treatment response.

The present study indicates that genetic risk for ADHD and schizophrenia in the general population is associated with a persistent, early-onset trajectory of depressive symptoms. Such effects could operate through overlapping biological pathways as well as evocative gene-environment correlation where genetic factors influence traits which then affect environmental exposures (e.g. victimization) associated with depression. Irritability, which is common in children with ADHD and other neurodevelopmental disorders, is indexed by genetic risk for ADHD in youth[69], and has been shown to increase risk for later depression[70,71] may be a potential route through which ADHD genetic risk increases the likelihood of mood problems. Among those with early-onset depression, we did not identify the equal gender ratio of affected males and females that has often been reported when depression onset is very early[4,72]. This was somewhat surprising. Several factors may have contributed to this. First, some research suggests that depression is particularly likely in

females with neurodevelopmental disorders which may imply that high neurodevelopmental risk is more likely to manifest as mood disorder in females[24,47,73]. Second, while it is generally accepted that self-reports of adolescent mood (as used in the present study) are reliable, children with neurodevelopmental disorders who are predominately male may under-report their mood symptoms compared to typically developing children[74]. This raises the possibility that the reliance on self-reported mood necessary in the present study due to repeated longitudinal assessments (see below) may mean that some individuals at high neurodevelopmental risk may have been misclassified. Finally, polygenic risk scores alone are unlikely to be able to reliably classify children's risk of developing different types of depression trajectories. However, collectively results converge to suggest that neurodevelopmental phenotypes (ADHD, social communication and pragmatic language difficulties) and neurodevelopmental genetic risk indicates a greater probability of an early-onset depression trajectory. Phenotypic childhood neurodevelopmental problems were markedly increased in the early-adolescent-onset group (by 5 to 7-fold) compared to the "typical" depression trajectory. Studies with follow-up further into adult life will help to clarify the adult mental health outcomes of these groups.

Strengths of this study include the repeated-measures longitudinal design where depression was assessed using exactly the same measure and informant. Typically, longitudinal studies include changes in measurement and informant, in particular, as children grow-up the informant tends to change from the parent to the young person themselves. This provides a challenge to studies seeking to examine the development of symptoms over time because changes of measurement and informant can affect results. This invariance of measurement over time is an important strength. A limitation is that like many longitudinal studies, ALSPAC suffers from non-random attrition over time (eTable 3). This is likely to result in conservative estimates of the prevalence of the elevated depression trajectory groups. We used a number of approaches to deal with missing data including FIML in trajectory modelling and inverse probability weighting (IPW) for tests of association. The

pattern of results replicated using IPW. It should be noted nonetheless that the missing data assumption made in our analyses is that there are not systematic differences between those who do and do not provide trajectory data and membership in the sample after conditioning on the other variables in the model (e.g. PRS and variables included in the IPW analysis). Depression was assessed using self-reported questionnaire rather than clinical assessment. Nonetheless, subthreshold symptoms are associated with impairment and subsequent MDD[2-4]. We focused on the full sample rather than examining gender differences although results were similar when carried out separately for males and females (results available from first author). It was not possible to investigate rates of mania or bipolar disorder in the trajectory groups. However, evidence is inconsistent on the link with early-onset depression and bipolar disorder[13,15,28]. The follow-up period in this study was limited to early adult life. A final limitation is that polygenic risk scores are weak predictors and only explain a small to modest proportion of phenotypic variance as they do in the present paper. However they do provide a useful biological indicator of genetic liability[75].

In summary, findings suggest etiologically distinct trajectories of depressive symptoms in youth dependent on age-at-onset and that neurodevelopmental genetic risk contributes to very early onset depression.

Figure 1. Developmental trajectories of depressive symptoms

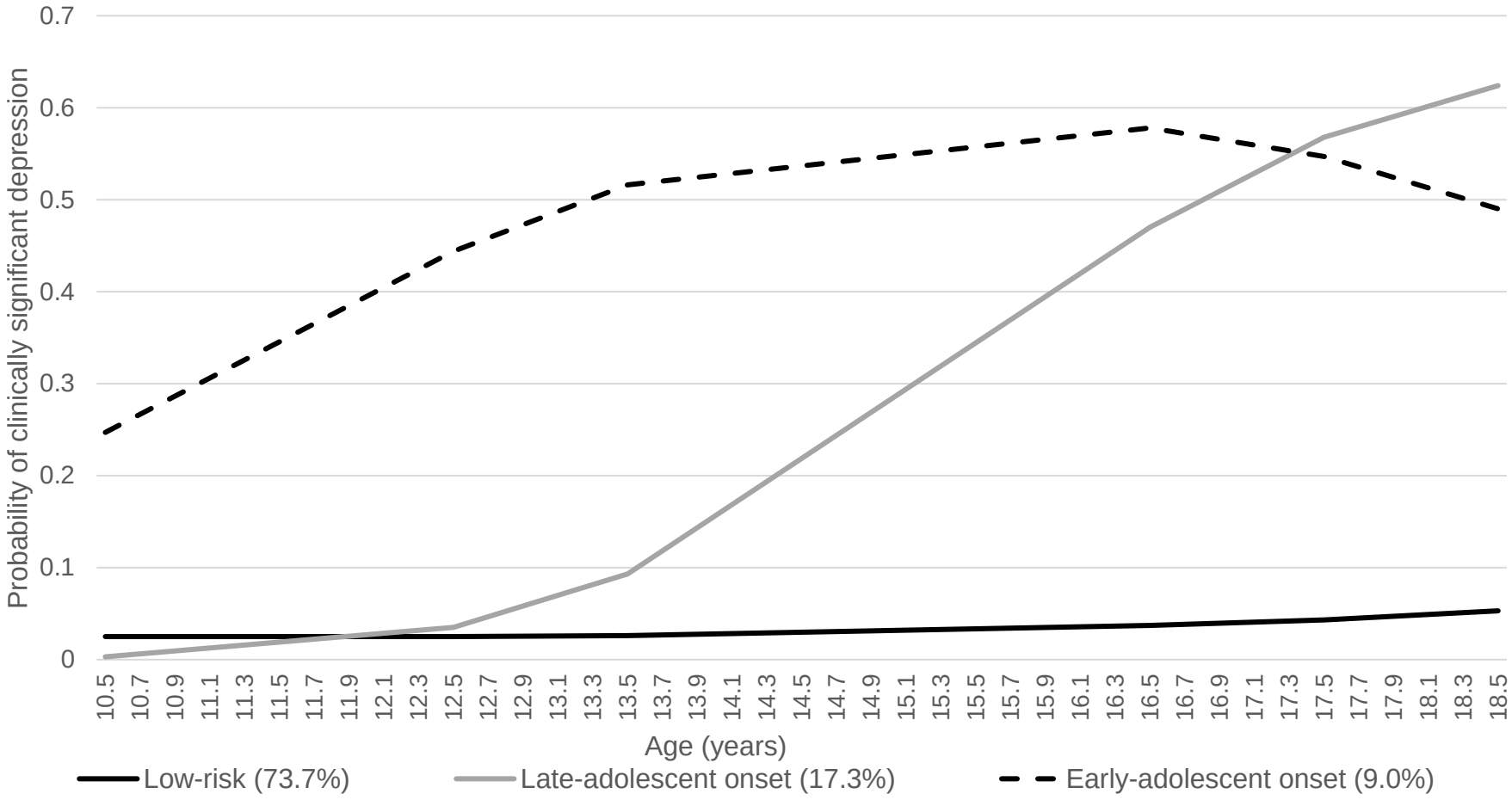

Table 1. Associations of polygenic risk scores with trajectory classes

		Early-adolescent-onset (9.0%) OR	95% CI	p	Late-adolescent-onset (17.3%) OR	95% CI	p
Univariate associations	MDD PRS	1.24	1.06, 1.46	.007	1.27	1.09, 1.48	.003
	Schizophrenia PRS	1.22	1.04, 1.43	.013	.95	.82, 1.11	.555
	ADHD PRS	1.32	1.13, 1.54	<.001	.94	.80, 1.11	.482
Multivariate associations	MDD PRS	1.16	.98, 1.36	.086	1.31	1.12, 1.53	.001
	Schizophrenia PRS	1.19	1.01, 1.41	.040	.93	.79, 1.10	.391
	ADHD PRS	1.27	1.08, 1.50	.003	.90	.76, 1.07	.229

Footnote to Table 1: Low class as the reference. OR= odds ratio for 1 standard deviation unit change, MDD = major depressive disorder, PRS = polygenic risk score. Late vs. early (multivariate analyses) MDD OR=1.13 (.88-1.46), p=.334; schizophrenia PRS OR=.78 (.60-1.01), p=.065, ADHD PRS OR=.71 (.55-.92), p=0.009

Table 2: phenotypic associations with trajectory class

Classes	Early-adolescent-onset (9.0%) % or OR	p	Late-adolescent-onset (17.3%) % or OR	p	Difference between early-adolescent and later-adolescent onset classes
Gender (%)	74.3	<.001	73.2	<.001	χ^2 = .015 (1), p=.904
Maternal education (completed A-levels) (%)	39.1	.012	34.9	.001	χ^2 = .707 (1), p=.440
Childhood ADHD (%)	6.3	.008	0.9	.365	χ^2 = 6.837 (1), p=.009
Pragmatic language difficulties	.63 (.55, .71)	<.001	.82 (.72, .94)	.006	OR = 1.31, p=.004 χ^2 = 11.709(1), p=.001 (for cut-point)
Social communication difficulties	1.50 (1.34, 1.68)	<.001	1.01 (.87, 1.18)	0.855	OR= .68, p<.001 χ^2 = 18.819(1), p=.001 (for cut-point)
Psychotic experiences (12 yrs)	1.47 (1.35, 1.61)	<.001	0.89 (.64, 1.22)	.455	OR=.60, p=.003
Psychotic experiences (17 yrs)	1.57 (1.36, 1.80)	<.001	1.54 (1.33, 1.79)	<.001	OR=0.99, p=.740

Footnote to Table 2: Continuous scores are standardized so odds ratios are for one standard deviation increase. Social communication score – higher scores represent more problems; pragmatic language score – lower scores represent more difficulties. Low group is the reference

group except for tests of comparison between early-adolescent and later-adolescent onset groups where the early-adolescent onset group is the reference group. χ^2 tests of difference for social communication and pragmatic language difficulties used the established clinical cut-points for identifying problems (eAppendix).

1. Vos T, Flaxman AD, Naghavi M, et al. Years lived with disability (YLDs) for 1160 sequelae of 289 diseases and injuries 1990-2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet.* 2012;380(9859):2163-2196.
2. Angold A, Costello EJ, Farmer EM, Burns BJ, Erkanli A. Impaired but undiagnosed. *Journal of the American Academy of Child and Adolescent Psychiatry.* 1999;38(2):129-137.
3. Johnson J, Weissman MM, Klerman GL. Service utilization and social morbidity associated with depressive symptoms in the community. *Jama.* 1992;267(11):1478-1483.
4. Thapar A, Collishaw S, Pine DS, Thapar AK. Depression in adolescence. *Lancet.* 2012;379(9820):1056-1067.
5. Rohde P, Lewinsohn PM, Klein DN, Seeley JR, Gau JM. Key Characteristics of Major Depressive Disorder Occurring in Childhood, Adolescence, Emerging Adulthood, Adulthood. *Clinical psychological science : a journal of the Association for Psychological Science.* 2013;1(1).
6. Weissman MM, Wickramaratne P, Nomura Y, Warner V, Pilowsky D, Verdeli H. Offspring of depressed parents: 20 years later. *The American journal of psychiatry.* 2006;163(6):1001-1008.
7. Patton GC, Coffey C, Romaniuk H, et al. The prognosis of common mental disorders in adolescents: a 14-year prospective cohort study. *Lancet.* 2014;383(9926):1404-1411.
8. Musliner KL, Trabjerg BB, Waltoft BL, et al. Parental history of psychiatric diagnoses and unipolar depression: a Danish National Register-based cohort study. *Psychological medicine.* 2015;45(13):2781-2791.
9. Lieb R, Isensee B, Hofler M, Pfister H, Wittchen HU. Parental major depression and the risk of depression and other mental disorders in offspring: a prospective-longitudinal community study. *Archives of general psychiatry.* 2002;59(4):365-374.
10. Rhebergen D, Lamers F, Spijker J, de Graaf R, Beekman AT, Penninx BW. Course trajectories of unipolar depressive disorders identified by latent class growth analysis. *Psychological medicine.* 2012;42(7):1383-1396.
11. Rice F, Harold G, Thapar A. The genetic aetiology of childhood depression: a review. *Journal of child psychology and psychiatry, and allied disciplines.* 2002;43(1):65-79.
12. Flint J, Kendler KS. The genetics of major depression. *Neuron.* 2014;81(3):484-503.
13. Harrington R, Rutter M, Weissman M, et al. Psychiatric disorders in the relatives of depressed probands. I. Comparison of prepubertal, adolescent and early adult onset cases. *Journal of affective disorders.* 1997;42(1):9-22.
14. Rutter M, Kim-Cohen J, Maughan B. Continuities and discontinuities in psychopathology between childhood and adult life. *Journal of child psychology and psychiatry, and allied disciplines.* 2006;47(3-4):276-295.
15. Jaffee SR, Moffitt TE, Caspi A, Fombonne E, Poulton R, Martin J. Differences in early childhood risk factors for juvenile-onset and adult-onset depression. *Archives of general psychiatry.* 2002;59(3):215-222.
16. Eaves LJ, Silberg JL, Meyer JM, et al. Genetics and developmental psychopathology: 2. The main effects of genes and environment on behavioral problems in the Virginia Twin Study of Adolescent Behavioral Development. *Journal of child psychology and psychiatry, and allied disciplines.* 1997;38(8):965-980.
17. Thapar A, McGuffin P. A twin study of depressive symptoms in childhood. *The British journal of psychiatry : the journal of mental science.* 1994;165(2):259-265.
18. Rice F, Harold GT, Thapar A. Assessing the effects of age, sex and shared environment on the genetic aetiology of depression in childhood and adolescence. *Journal of child psychology and psychiatry, and allied disciplines.* 2002;43(8):1039-1051.

19. Power RA, Tansey KE, Buttenschon HN, et al. Genome-wide Association for Major Depression Through Age at Onset Stratification: Major Depressive Disorder Working Group of the Psychiatric Genomics Consortium. *Biological psychiatry.* 2017;81(4):325-335.
20. Riglin L, Collishaw S, Richards A, et al. Schizophrenia risk alleles and neurodevelopmental outcomes in childhood: a population-based cohort study. *The lancet Psychiatry.* 2017;4(1):57-62.
21. Craddock N, Owen MJ. The Kraepelinian dichotomy - going, going... but still not gone. *The British journal of psychiatry : the journal of mental science.* 2010;196(2):92-95.
22. Owen MJ. New approaches to psychiatric diagnostic classification. *Neuron.* 2014;84(3):564-571.
23. Kessler RC, Adler LA, Berglund P, et al. The effects of temporally secondary co-morbid mental disorders on the associations of DSM-IV ADHD with adverse outcomes in the US National Comorbidity Survey Replication Adolescent Supplement (NCS-A). *Psychological medicine.* 2014;44(8):1779-1792.
24. Avenevoli S, Swendsen J, He JP, Burstein M, Merikangas KR. Major depression in the national comorbidity survey-adolescent supplement: prevalence, correlates, and treatment. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2015;54(1):37-44 e32.
25. Angold A, Costello EJ, Erkanli A. Comorbidity. *Journal of child psychology and psychiatry, and allied disciplines.* 1999;40(1):57-87.
26. Demontis D, Walters RK, Martin J, et al. Discovery Of The First Genome-Wide Significant Risk Loci For ADHD. *bioRxiv.* 2017.
27. Cross-Disorder Group of the Psychiatric Genomics C, Lee SH, Ripke S, et al. Genetic relationship between five psychiatric disorders estimated from genome-wide SNPs. *Nature genetics.* 2013;45(9):984-994.
28. Kovacs M, Obrosky S, George C. The course of major depressive disorder from childhood to young adulthood: Recovery and recurrence in a longitudinal observational study. *Journal of affective disorders.* 2016;203:374-381.
29. Boyd A, Golding J, Macleod J, et al. Cohort Profile: the 'children of the 90s'--the index offspring of the Avon Longitudinal Study of Parents and Children. *International journal of epidemiology.* 2013;42(1):111-127.
30. Fraser A, Macdonald-Wallis C, Tilling K, et al. Cohort Profile: the Avon Longitudinal Study of Parents and Children: ALSPAC mothers cohort. *International journal of epidemiology.* 2013;42(1):97-110.
31. Thabrew H, Stasiak K, Bavin LM, Frampton C, Merry S. Validation of the Mood and Feelings Questionnaire (MFQ) and Short Mood and Feelings Questionnaire (SMFQ) in New Zealand help-seeking adolescents. *International journal of methods in psychiatric research.* 2018.
32. Costello EJ, Angold A. Scales to assess child and adolescent depression: checklists, screens, and nets. *Journal of the American Academy of Child and Adolescent Psychiatry.* 1988;27(6):726-737.
33. Thapar A, McGuffin P. Validity of the shortened Mood and Feelings Questionnaire in a community sample of children and adolescents: a preliminary research note. *Psychiatry research.* 1998;81(2):259-268.
34. Neale BM, Medland SE, Ripke S, et al. Meta-analysis of genome-wide association studies of attention-deficit/hyperactivity disorder. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2010;49(9):884-897.
35. Schizophrenia Working Group of the Psychiatric Genomics C. Biological insights from 108 schizophrenia-associated genetic loci. *Nature.* 2014;511(7510):421-427.
36. Wray NR, Ripke S, Mattheisen M, et al. Genome-wide association analyses identify 44 risk variants and refine the genetic architecture of major depression. *Nature genetics.* 2018;50(5):668-681.

37. APA. *Diagnostic and Statistical Manual of Mental Disorders: DSM-IV-TR.* Washington, DC.: American Psychiatric Press; 2000.
38. Muthén LK, Muthén BO. *MPlus User's Guide.* 7th. ed. Los Angeles, CA. 2012.
39. Muthen B, Muthen LK. Integrating person-centered and variable-centered analyses: Growth mixture modeling with latent trajectory classes. *Alcohol Clin Exp Res.* 2000;24(6):882-891.
40. Asparouhov T, B. M. Auxiliary variables in mixture modeling: Three-step approaches using Mplus. *Structural Equation Modeling: A Multidisciplinary Journal* 2014;21(3):329-341.
41. Heron JE, Croudace TJ, Barker ED, Tilling KA. A comparison of approaches for assessing covariate effects in latent class analysis. *Longitudinal and Life Course Studies.* 2015;6(4):420-434.
42. van de Schoot R, Sijbrandij M, Winter SD, SDepaoli S, Vermunt JK. The GRoLTS-Checklist: Guidelines for Reporting on Latent Trajectory Studies. *Structural Equation Modeling: A Multidisciplinary Journal.* 2017;24(3):451-467.
43. Berlin KS, Parra GR, Williams NA. An introduction to latent variable mixture modeling (part 2): longitudinal latent class growth analysis and growth mixture models. *Journal of pediatric psychology.* 2014;39(2):188-203.
44. Seaman SR, White IR. Review of inverse probability weighting for dealing with missing data. *Statistical methods in medical research.* 2013;22(3):278-295.
45. Lewis G, Pelosi AJ, Araya R, Dunn G. Measuring psychiatric disorder in the community: a standardized assessment for use by lay interviewers. *Psychological medicine.* 1992;22(2):465-486.
46. Riglin L, Collishaw S, Thapar AK, et al. Association of genetic risk variants with attention-deficit/hyperactivity disorder trajectories in the general population. *JAMA psychiatry.* 2016;Vol.73(12):pp.
47. Martin J, Hamshere ML, Stergiakouli E, O'Donovan MC, Thapar A. Genetic risk for attention-deficit/hyperactivity disorder contributes to neurodevelopmental traits in the general population. *Biological psychiatry.* 2014;76(8):664-671.
48. McGrath JJ, Saha S, Al-Hamzawi A, et al. The Bidirectional Associations Between Psychotic Experiences and DSM-IV Mental Disorders. *The American journal of psychiatry.* 2016;173(10):997-1006.
49. Jones HJ, Stergiakouli E, Tansey KE, et al. Phenotypic Manifestation of Genetic Risk for Schizophrenia During Adolescence in the General Population. *JAMA psychiatry.* 2016;73(3):221-228.
50. Kessler RC, Berglund P, Demler O, Jin R, Merikangas KR, Walters EE. Lifetime prevalence and age-of-onset distributions of DSM-IV disorders in the National Comorbidity Survey Replication. *Archives of general psychiatry.* 2005;62(6):593-602.
51. Verduijn J, Milaneschi Y, Peyrot WJ, et al. Using Clinical Characteristics to Identify Which Patients With Major Depressive Disorder Have a Higher Genetic Load for Three Psychiatric Disorders. *Biological psychiatry.* 2017;81(4):316-324.
52. Wickramaratne PJ, Weissman MM. Onset of psychopathology in offspring by developmental phase and parental depression. *Journal of the American Academy of Child and Adolescent Psychiatry.* 1998;37(9):933-942.
53. Harrington R. Adolescent depression: same or different? *Archives of general psychiatry.* 2001;58(1):21-22.
54. Weissman MM, Wolk S, Wickramaratne P, et al. Children with prepubertal-onset major depressive disorder and anxiety grown up. *Archives of general psychiatry.* 1999;56(9):794-801.
55. Harrington R, Fudge H, Rutter M, Pickles A, Hill J. Adult outcomes of childhood and adolescent depression. I. Psychiatric status. *Archives of general psychiatry.* 1990;47(5):465-473.

56. Harrington R, Rutter M, Fombone E. Developmental pathways in depression: Multiple meanings, antecedents, and endpoints. *Development and Psychopathology.* 1996;8:601-616.
57. Sigurdsson E, Van Os J, Fombonne E. Are impaired childhood motor skills a risk factor for adolescent anxiety? Results from the 1958 U.K. birth cohort and the National Child Development Study. *The American journal of psychiatry.* 2002;159(6):1044-1046.
58. van Os J, Jones P, Lewis G, Wadsworth M, Murray R. Developmental precursors of affective illness in a general population birth cohort. *Archives of general psychiatry.* 1997;54(7):625-631.
59. Ljung T, Chen Q, Lichtenstein P, Larsson H. Common etiological factors of attention-deficit/hyperactivity disorder and suicidal behavior: a population-based study in Sweden. *JAMA psychiatry.* 2014;71(8):958-964.
60. Hammerton G, Zammit S, Mahedy L, et al. Pathways to suicide-related behavior in offspring of mothers with depression: the role of offspring psychopathology. *Journal of the American Academy of Child and Adolescent Psychiatry.* 2015;54(5):385-393.
61. Nock MK, Green JG, Hwang I, et al. Prevalence, correlates, and treatment of lifetime suicidal behavior among adolescents: results from the National Comorbidity Survey Replication Adolescent Supplement. *JAMA psychiatry.* 2013;70(3):300-310.
62. Klein RG, Mannuzza S, Olazagasti MA, et al. Clinical and functional outcome of childhood attention-deficit/hyperactivity disorder 33 years later. *Archives of general psychiatry.* 2012;69(12):1295-1303.
63. Capaldi DM. Co-occurence of conduct problems and depressive symptoms in early adolescent boys: II. A 2 year follow-up at Grade 8. *Development and Psychopathology.* 1992;4:125-144.
64. Biederman J, Mick E, Faraone SV. Depression in attention deficit hyperactivity disorder (ADHD) children: "true" depression or demoralization? *Journal of affective disorders.* 1998;47(1-3):113-122.
65. Hazell P, Mirzaie M. Tricyclic drugs for depression in children and adolescents. *Cochrane Database of Systematic Reviews.* 2013(6).
66. Hazell P, O'Connell D, Heathcote D, Robertson J, Henry D. Efficacy of tricyclic drugs in treating child and adolescent depression: a meta-analysis. *Bmj.* 1995;310(6984):897-901.
67. Hetrick SE, McKenzie JE, Cox GR, Simmons MB, Merry SN. Newer generation antidepressants for depressive disorders in children and adolescents. . *Cochrane Database of Systematic Reviews.* 2012;11.
68. Hetrick SE, McKenzie JE, Merry SN. The use of SSRIs in children and adolescents. *Current opinion in psychiatry.* 2010;23(1):53-57.
69. Riglin L, Eyre O, Cooper M, et al. Investigating the genetic underpinnings of early-life irritability. *Translational psychiatry.* 2017;7(9):e1241.
70. Stringaris A, Cohen P, Pine DS, Leibenluft E. Adult outcomes of youth irritability: a 20-year prospective community-based study. *The American journal of psychiatry.* 2009;166(9):1048-1054.
71. Rice F, Sellers R, Hammerton G, et al. Antecedents of New-Onset Major Depressive Disorder in Children and Adolescents at High Familial Risk. *JAMA psychiatry.* 2017;74(2):153-160.
72. Maughan B, Collishaw S, Stringaris A. Depression in childhood and adolescence. *Journal of the Canadian Academy of Child and Adolescent Psychiatry = Journal de l'Academie canadienne de psychiatrie de l'enfant et de l'adolescent.* 2013;22(1):35-40.
73. Martin J, Walters RK, Demontis D, et al. A Genetic Investigation of Sex Bias in the Prevalence of Attention-Deficit/Hyperactivity Disorder. *Biological psychiatry.* 2017.
74. Fraser A, Cooper M, Agha SS, et al. The presentation of depression symptoms in attention-deficit/hyperactivity disorder: comparing child and parent reports. *Child and Adolescent Mental Health* 2017.

75. Kendler KS. The Schizophrenia Polygenic Risk Score: To What Does It Predispose in Adolescence? *JAMA psychiatry.* 2016;73(3):193-194.

Article Title: Early onset depression: characterising developmental trajectories and the role of psychiatric genetic risk variants

Authors: Frances Rice, PhD [1], Lucy Riglin, PhD [1], Ajay K Thapar, PhD, MD [1], Jon Heron, PhD [2] , Richard Anney, PhD [1], Michael C O'Donovan, PhD, MD [1], Anita Thapar, PhD, MD [1]

1 MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Cardiff University, UK

2 School of Social and Community Medicine, University of Bristol, UK

Correspondence:

F Rice

MRC Centre for Neuropsychiatric Genetics and Genomics, Division of Psychological Medicine and Clinical Neurosciences, Hadyn Ellis Building, Maindy Road, Cardiff University, CF24 4HQ, UK

Email: ricef2@cardiff.ac.uk

Phone: 00 44 (0)29 20 688384

Author contributions

Conceived the paper: FR, AKT, LR, JH, AT

Drafted the paper: FR, LR, RA

Critically revised the paper FR, AKT, LR, JH, RA, AT, MO

Statistical analysis LR, AKT, RA, FR

Statistical advice JH

FR and RA had full access to all the data in the study and take responsibility for the accuracy of the statistical analysis

Revision date: 6th September 2018

Word count (text only): 2999

All authors approved the final version

Email addresses for other authors:

ThaparAK@cardiff.ac.uk

RiglinL@cardiff.ac.uk

Jon.Heron@bristol.ac.uk

AnneyR@cardiff.ac.uk

Thapar@cardiff.ac.uk

ODonovanMC@cardiff.ac.uk

Conflict of interest disclosures

None

Acknowledgements: This study was supported by a seedcorn grant from the MRC Centre for Neuropsychiatric Genetics and Genomics and the Medical Research Council MR/R004609/1.

Role of the Funder/Sponsor: The funding source had no role in the design and conduct of the study; collection, management, analysis and interpretation of the data; preparation, review, or approval of the manuscript; and decision to submit the manuscript for publication.

Additional contributions

We acknowledge the members of the Psychiatric Genomics Consortium for the publicly available data used as the discovery samples in this article. We thank the Bipolar Disorder Working Group of the Psychiatric Genomics Consortium for providing the bipolar disorder summary statistics used in this study. We are extremely grateful to all the families who took part in this study, the midwives for their help in recruiting them, and the whole ALSPAC team, which includes interviewers, computer and laboratory technicians, clerical workers, research scientists, volunteers, managers, receptionists and nurses.

Funding

The UK Medical Research Council and Wellcome (Grant ref: 102215/2/13/2) and the University of Bristol provide core support for ALSPAC. A comprehensive list of grants funding is available on the ALSPAC website. This research was specifically funded by Wellcome Trust 08426812/Z/07/Z, Wellcome Trust and MRC 092731 which funded data collection on depression. This publication is the work of the authors; Frances Rice and Richard Anney will serve as guarantors for the contents of this paper. Genome-wide association study data were generated by Sample Logistics and Genotyping Facilities at

Wellcome Sanger Institute and LabCorp (Laboratory Corporation of America) using support from 23andMe.

LR is supported by the Wellcome Trust 204895/Z/16/Z. FR receives funding from the Medical Research Council MR/R004609/1.